









# A Real-World Study of Optimal Treatment with Anlotinib First-Line Therapy in Advanced Hepatocellular Carcinoma

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**Purpose:** To observe the efficacy and safety of anlotinib as a first-line treatment for patients with advanced hepatocellular carcinoma (aHCC) in a real-world environment, explore the optimal treatment regimen for patients with aHCC using anlotinib as a first-line treatment.

**Patients and Methods:** Data from 62 patients with aHCC who received anlotinib single-drug first-line therapy between February 2019 and November 2021. Patients received anlotinib monotherapy, which may be interrupted or discontinued or changed in the event of unacceptable or severe adverse events (AEs) or failure to inhibit tumor progression. The primary endpoint was progression-free survival (PFS) and the secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety.

**Results:** Among the 62 patients, in the best overall response assessment, there were 12 with complete response (CR; 19.4%), 17 with partial response (PR; 27.4%), 25 with stable disease (SD; 40.3%), and 8 with progressive disease (PD; 14.5%). The ORR and DCR were 46.8% and 87.1%, respectively. Among the 11 patients who received tyrosine kinase inhibitors (TKIs) combined with programmed death 1 (PD-1) inhibitors after disease progression, three (27.3%) had CR, one (9.1%) had PR, three (27.3%) had SD, and four (36.4%) had PD. Therefore, the ORR and DCR were 36.4% and 63.6%, respectively. The median PFS for anlotinib monotherapy was 7.37 months (95% confidence interval [CI]: 5.88–8.86) and the median OS did not reach. AEs occurred in 95.2% of patients during anlotinib monotherapy, with the most common being thrombocytopenia (51.6%). The incidence of grade  $\geq 3$  AEs was 38.7%.

**Conclusion:** Anlotinib is effective and well-tolerated as a first-line treatment for patients with aHCC. Treatment with TKIs and PD-1 inhibitors after disease progression has also shown preliminary efficacy and safety; therefore, sequential therapy with anlotinib-TKIs and PD-1 inhibitors may be an effective treatment for patients with aHCC.

**Keywords:** hepatocellular carcinoma, anlotinib, sequential therapy, real world

## Introduction

Primary liver cancer is one of the six most common cancers and the third leading cause of cancer-related death worldwide in 2020.<sup>1</sup> The number of new cases and deaths due to liver cancer worldwide was approximately 854,000 and 810,000 in 2015,<sup>2</sup> 841,000 and 782,000 in 2018,<sup>3</sup> and 906,000 and 830,000 in 2020,<sup>1</sup> with the ratio of mortality to morbidity approaching 1. Because of the high incidence of hepatitis B virus infection, the morbidity and mortality of liver cancer in China remain high. Primary liver cancer is the fifth most common cancer in China, with the second

highest mortality rate and is more commonly found in younger people.<sup>4–7</sup> Hepatocellular carcinoma (HCC) is the main pathological type of primary liver cancer, accounting for 75–85% of cases.<sup>8</sup> Current treatment options for HCC include liver transplantation, surgical resection, and local and systemic therapy. Because of the insidious onset of liver cancer, most patients already have advanced stage disease when diagnosed, making radical treatment, such as surgery and liver transplantation, impossible. Without effective treatment, the natural survival time is only 3–4 months,<sup>9,10</sup> and the overall 5-year survival rate is 10–15%,<sup>11,12</sup> posing a serious threat to the life and health of Chinese people.

Sorafenib was approved for the treatment of patients with advanced hepatocellular carcinoma (aHCC). Although the median time to progress (mTTP) of aHCC is only 2.8 months and 5.5 months, and the median overall survival (mOS) only 6.5 months and 10.7 months,<sup>13,14</sup> sorafenib has been the only targeted drug for first-line treatment of aHCC for more than ten years and its dominance was not broken until the approval of lenvatinib in 2018. The median progression-free survival (mPFS) with lenvatinib treatment was 7.2–7.4 months.<sup>13,14</sup> Atezolizumab combined with bevacizumab, regorafenib, apatinib, pembrolizumab, and camrelizumab has been successively approved for the treatment of aHCC.<sup>15–19</sup> Although the combination of immune checkpoint inhibitors (ICIs) and different antiangiogenic tyrosine kinase inhibitors (TKIs) has some efficacy in patients with aHCC, combination therapy is more prone to lead to severe adverse reactions than monotherapy,<sup>15</sup> and the suspension of treatment or dose reduction caused by severe adverse reactions may affect therapeutic efficacy.<sup>20</sup> Combination therapy greatly increases the economic burden on patients with cancer. Therefore, better tolerability protocols should be explored for the treatment of patients with aHCC to minimize side effects while maximizing therapeutic effects.

Anlotinib (produced by Zhengdatianqing Pharmaceutical Group Co., LTD., Lianyungang City, Jiangsu Province, China) is a novel multitarget oral tyrosine kinase inhibitor that has been approved in China for the treatment of non-small cell lung cancer, small cell lung cancer, soft tissue sarcoma, and medulloid thyroid cancer and has received level 4C evidence in the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 edition). The experimental results showed that anlotinib was superior to sunitinib, sorafenib, and nidanim in terms of antiangiogenesis.<sup>21</sup> The targets of anlotinib include fibroblast growth factor receptor 1–4 (FGFR1–4), vascular endothelial growth factor receptor 1–3 (VEGFR1–3), platelet-derived growth factor receptor  $\alpha$  and  $\beta$  (PDGFR $\alpha$ ,  $\beta$ ), c-kit, and RET.<sup>22,23</sup> Anlotinib highly specifically inhibit VEGFR2.<sup>24</sup> Anlotinib has wide inhibitory effects that are similar to regorafenib inhibitory effects, thus suggesting a broad-spectrum antitumor activity compared to the other TKI.<sup>25</sup> Immune cells play a intricate role in the tumor microenvironment and tumor neoangiogenesis.<sup>26</sup> Anlotinib down-regulates the expression of PD-L1 on vascular endothelial cells (VECs) by inactivating AKT pathway, thereby increasing the ratio of CD8/FoxP3 inside tumor and improving the immune microenvironment to inhibit tumor growth.<sup>21,27</sup> Anlotinib has been shown to be effective and well-tolerated in many patients with HCC, and there are many cases of anlotinib in combination with immunotherapy in clinical practice.<sup>28–30</sup> In this study, we aimed to observe the efficacy and safety of anlotinib as a first-line treatment for aHCC in the real world, explore the effects of other treatments for patients with disease progression, and explore the optimization of treatment options for such patients in the real world.

## Materials and Methods

### Etonogestrel Implant

Data from 62 patients with aHCC who received anlotinib single-drug first-line therapy at the First Affiliated Hospital of Zhengzhou University between February 2019 and November 2021 were retrospectively collected. The inclusion criteria were as follows:<sup>1</sup> age  $\geq 18$  years;<sup>2</sup> non-resectable HCC diagnosed pathologically or clinically;<sup>3</sup> at least one measurable lesion according to the RECIST 1.1 criteria;<sup>4</sup> Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1;<sup>5</sup> Child–Pugh score for liver function  $\leq 9$ ;<sup>6</sup> Barcelona Clinic Liver Cancer (BCLC) stage B or C; and<sup>7</sup> expected survival  $\geq 3$  months. The exclusion criteria were:<sup>1</sup> history of solid organ transplantation or bone marrow suppression;<sup>2</sup> systemic treatment required for acute autoimmune diseases; and<sup>3</sup> the presence of autoimmune defects, the need for steroids, or other immunosuppressive treatment.<sup>4</sup> Prior systemic antitumor therapy with chemotherapy drugs, targeted drugs, and ICIs. As the clinical data and information of patients were collected retrospectively in an anonymized manner, and the data were confirmed to be anonymous and confidential. This study complied with the Declaration of Helsinki, and exempting the

signing of informed consent would not adversely affect the rights and welfare of the subjects. Therefore, an informed consent exemption was obtained from the Ethics Committee of Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University. This study was approved by the Ethics Committee of Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University. (approval no. 2022-KY-0113-002).

## Assessment of Efficacy and Adverse Events

Anlotinib was initially given at 8/10/12 mg/d by the physician in charge after a comprehensive assessment of the patient's condition, orally before breakfast for 2 weeks, followed by 1 week of withdrawal and 3 weeks (21 days) of treatment. When unacceptable or severe AEs were present or tumor progression was unchecked, the treatment regimen were potentially interrupted, stopped, or modified.

Imaging examinations were performed using enhanced computed tomography (CT), magnetic resonance imaging (MRI), or other available imaging techniques from week 4 following the initiation of anlotinib therapy and every 8 to 12 weeks thereafter. Changes in tumor size were assessed using RECIST 1.1. They were classified into complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

AEs were collected in detail and evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 5.0). When grade  $\geq 3$  AEs occurred, the physician in charge, based on the instructions and clinical experience, decided to reduce the dose, discontinue treatment, or permanently discontinue the drug until the AEs subsided to level 1 or 2, which can be controlled by the drug.

The primary endpoint of the study was progression-free survival (PFS), and the secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. PFS was defined as the time between the onset of treatment and the appearance of objective tumor progression or death; OS was defined as the time between initial treatment and death from any cause; ORR was calculated as the sum of the percentage of complete and partial responses; and DCR was calculated as the sum of the percentage of stable disease, complete response, and partial response.

## Statistical Analysis

Statistical data are expressed as percentages, and differences were analyzed using the  $\chi^2$  or Fisher's exact test. Non-normally distributed continuous data are described as medians. The Kaplan–Meier method was used to generate PFS curves, the Cox proportional risk model was used to analyze univariate and multivariate factors, and the hazard ratio (HR) and corresponding 95% confidence interval (CI) were obtained. Statistical significance was set at  $P < 0.05$ . All statistical analyses were performed using SPSS (version 26.0).

## Results

### Patient Characteristics

A total of 62 patients with aHCC who received anlotinib as first-line therapy in our hospital between February 2019 and November 2021 were enrolled in this study. Among the 62 patients, with a median age of 55.0 (38.0–78.0) years, 58 (93.5%) had hepatitis B, 1 (1.6%) had hepatitis C, 52 (83.9%) had received previous local or surgical treatment, 27 (43.5%) had portal venous thrombosis (PVT), 18 (29.0%) had extrahepatic metastasis (EHM), 18 (29.0%) had liver occupation greater than 50%, and 42 (67.7%) were evaluated as being BCLC stage C. Fifty-five (88.7%) patients were men. Seventeen (27.4%) patients had Child–Pugh class B liver function, among whom 14 (22.6%) had a Child–Pugh score of 8–9. The baseline patient characteristics are shown in [Table 1](#).

A total of 21 patients experienced a change in treatment regimen because of disease progression, including 11 patients whose treatment regimen changed to TKIs combined with PD-1 inhibitors and had  $\geq 2$  radiographic evaluations.

### Efficacy

#### PFS for Anlotinib Monotherapy and OS for Total Duration of Treatment

The median follow-up time was 13.3 months (5.47–35.03). The mPFS for anlotinib monotherapy was 7.37 months (95% CI: 5.85–8.89) ([Figure 1](#)). The mOS of all patients during the total follow-up period was not reached, greater than 13.27 months

**Table 1** Patient Demographics and Clinical Characteristics

	n=62		n=62
Sex		ECOG score	
Male	55 (88.7%)	0	51 (82.3%)
Female	7 (11.3%)	I	11 (17.7%)
Age (years)	55.0 (38.0–78.0)	BCLC stage	
31–45	6 (9.7%)	B	20 (32.3%)
46–60	38 (61.3%)	C	42 (67.7%)
60	18 (29.0%)	WBC ( $\times 10^9/L$ )	
Alcohol		$\leq 2.5$	8 (12.9%)
Yes	18 (29.0%)	2.5	54 (87.1%)
No	44 (71.0%)	PLT ( $\times 10^9/L$ )	
Hepatitis		$\leq 75$	18 (29.0%)
HBV	58 (93.5%)	$> 75$	44 (71.0%)
HCV	1 (1.6%)	ALB (g/L)	
No	3 (4.8%)	$\leq 35.0$	20 (32.3%)
PVT		$> 35.0$	42 (67.7%)
Yes	27 (43.5%)	TBIL ( $\mu\text{mol/L}$ )	
No	35 (56.5%)	$\leq 25.0$	48 (77.4%)
EHM		$> 25.0$	14 (22.6%)
Yes	18 (29.0%)	AFP (ng/mL)	
No	44 (71.0%)	$\leq 200$	40 (64.5%)
ALBI score (mean $\pm$ SD)		$> 200$	22 (35.5%)
1	20 (32.3%)/-3.05 $\pm$ 2.86	Child–Pugh class	
2	39 (62.9%)/-2.14 $\pm$ 0.36	A	45 (72.6%)
3	3 (4.8%)/-1.30 $\pm$ 0.52	B	17 (27.4%)

**Abbreviations:** PVT, portal venous thrombosis; EHM, extrahepatic metastasis; ALBI, albumin–bilirubin; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; WBC, white blood cells; PLT, platelets; ALB, albumin; TBIL, total bilirubin; AFP, Alpha–fetoprotein.

(95CI% 10.50–16.04), the 6-month survival rate was 100.0%, and the 1-year survival rate was 82.7%. At the cut-off date, 5 patients had a survival time of more than 2 years. Follow-up of 11 patients who changed treatment regimen to TKIs combined with PD-1 inhibitors showed that mOS was not achieved, greater than 17.00 months (95% CI: 10.24–23.77).

### Overall Response to Anlotinib Monotherapy

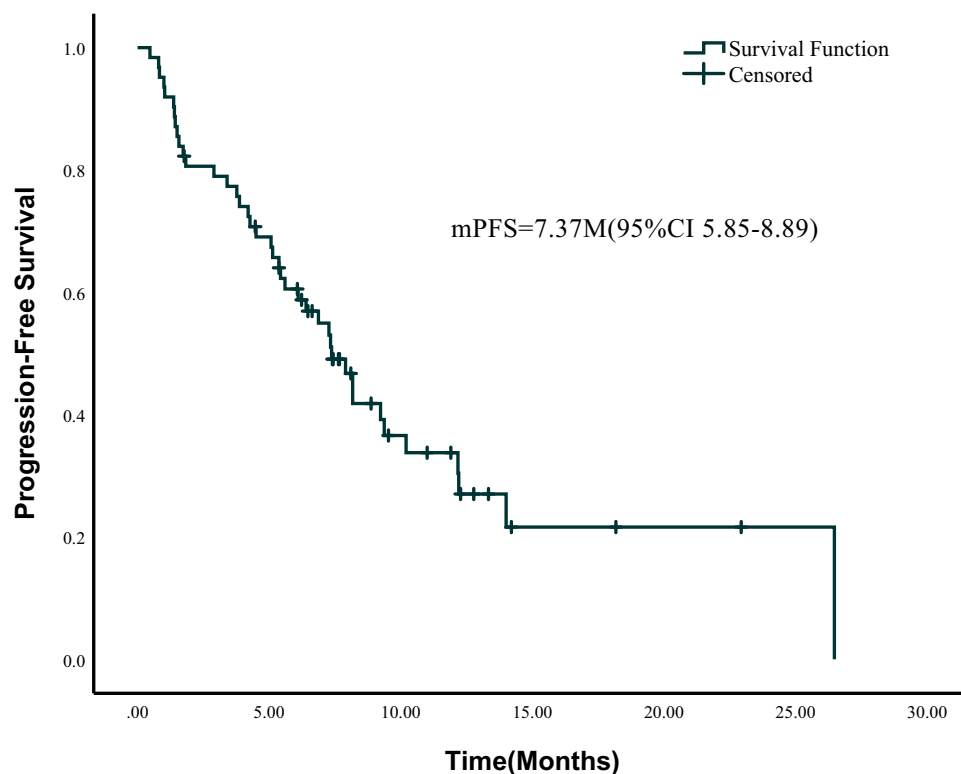
In the best overall response assessment, there were 12 (19.4%) patients with CR, 17 (27.4%) with PR, 25 (40.3%) with SD, and 8 (12.9%) with PD; the ORR and DCR were 46.8% and 87.1%, respectively (Table 2). The ORR and DCR were 43.5% and 83.9% at 3 months and 45.2% and 85.5% at 6 months, respectively.

### Subsequent Treatments

Among the 11 patients who received TKIs combined with PD-1 inhibitors after disease progression, three (27.3%) achieved CR, one (9.1%) achieved PR, three (27.3%) achieved SD, and four (36.4%) achieved PD. The ORR was 36.4%, and the DCR was 63.6% (Table 2).

### Factors Influencing PFS

Univariate Cox regression showed that BCLC grade, PVT, and EHM significantly correlated with PFS ( $P = 0.001$ ,  $0.033$ , and  $0.003$ , respectively). Multivariate Cox analysis showed that EHM (HR: 2.53, 95% CI: 1.19–5.36,  $P = 0.015$ ), PVT (HR: 1.61, 95% CI: 0.70–3.69,  $P = 0.262$ ), and BCLC class (HR: 1.97, 95% CI: 1.19–5.36,  $P = 0.204$ ), indicating that patients with EHM had a 2.53 times higher risk of disease progression relative to patients without EHM (Table 3).



**Figure 1** Progression-free survival curve.

## Alpha-Fetoprotein (AFP) Level Changes 1 Month After Anlotinib Monotherapy

AFP levels were determined one month after anlotinib administration. Eighteen patients with AFP levels within the normal range (<8.7 ng/mL) during treatment were excluded. The rate of change in AFP at 1 month was defined as follows: percentage change at 1 month = (AFP level at 1 month – initial AFP level)/initial AFP level. One month after initiation of treatment, 72.7% (32/44) of patients had lower AFP levels than at baseline, with a median AFP change rate of –26.0% (–97.0% to +135.0%).

## Adverse Events

During anlotinib monotherapy, four patients (6.5%) stopped taking anlotinib, one patient changed dressing because of intolerance to abdominal distention, one patient stopped taking anlotinib because of poor health condition and loss of appetite, and two patients had grade  $\geq 3$  gastrointestinal bleeding and were evaluated by a competent physician and

**Table 2** Overall Response to Treatment

	Anlotinib (n=62) <sup>a</sup>	TKIs+PD-I (n=11) <sup>b</sup>
CR	12 (19.4%)	3 (27.3%)
PR	17 (27.4%)	1 (9.1%)
SD	25 (40.3%)	3 (27.3%)
PD	8 (12.9%)	4 (36.4%)
ORR	29 (46.8%)	4 (36.4%)
DCR	54 (87.1%)	7 (63.6%)

**Notes:** <sup>a</sup>Overall response to anlotinib monotherapy. <sup>b</sup>Overall response to the regimen of TKIs combined with PD-I blockade after progression with anlotinib monotherapy.

**Abbreviations:** TKIs, tyrosine kinase inhibitors; PD-I, programmed death I; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

**Table 3** Multivariate Analysis of Factors Associated with PFS

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	p	HR	95% CI	P value
BCLC Stage	0.29	0.13–0.64	0.002	1.97	1.19–5.36	0.204
PVT	2.01	1.06–3.81	0.032	1.61	0.70–3.69	0.262
EHM	2.79	1.45–5.36	0.002	2.53	1.19–5.36	0.015

**Abbreviations:** BCLC, Barcelona Clinic Liver Cancer; PVT, portal venous thrombosis; EHM, extrahepatic metastasis.

stopped taking the drug. In eight patients (12.9%), the dosage was reduced because of AEs with the consent of the physician in charge. The incidence of AEs was 95.2% (59/62) and 38.7% (24/62) for grades 3 and above, respectively. The most common AEs were thrombocytopenia (51.6%), leukopenia (50.0%), hypertension and neutropenia (46.8%), fatigue (43.5%), hand-foot syndrome (41.9%), and total bilirubin (TBIL) elevation (37.1%). The incidence of grade  $\geq 3$  AEs was 38.7% (24/62), and the most common grade  $\geq 3$  AEs were hypertension (12.9%), TBIL elevation (9.7%), and neutropenia (7.9%). Grade  $\geq 3$  bleeding was gastrointestinal bleeding, and one patient died because of gastrointestinal bleeding (Table 4).

The percentage change in the Child–Pugh grade during anlotinib monotherapy is shown in Table 4. Before treatment, 45 (72.6%) of the 62 patients were Child–Pugh class A and 17 (27.4%) were Child–Pugh class B; at the end of anlotinib monotherapy/last follow-up, 35 patients (56.5%) were Child–Pugh class A, 20 (32.3%) were Child–Pugh class B, and 7 (11.3%) were Child–Pugh class C, the change in group distribution was statistically significantly different ( $P=0.030$ ).

**Table 4** Safety Profile

	Any Adverse Event (n=62)	AEs $\geq 3$ (n=62)
Any adverse event	59 (95.2%)	24 (38.7%)
HFS	26 (41.9%)	–
Hypertension	29 (46.8%)	8 (12.9%)
Diarrhea	21 (33.8%)	–
Belching	7 (11.3%)	–
Constipation	5 (8.1%)	–
Skin eruption	3 (4.8%)	–
Myodynia	1 (1.6%)	–
Fatigue	27 (43.5%)	–
Headache	4 (6.5%)	–
Hoarse	2 (3.2%)	–
Bleeding	12 (19.4%)	2 (3.2%)
Sinus tachycardia	1 (1.6%)	–
Leucopenia	31 (50.0%)	4 (6.5%)
Thrombocytopenia	32 (51.6%)	1 (1.6%)
Neutropenia	29 (46.8%)	5 (7.9%)
Lymphocytopenia	19 (30.6%)	3 (4.8%)
Cr elevation	4 (6.5%)	–
UA elevation	10 (16.1%)	–
ALT elevation	9 (14.5%)	–
AST elevation	14 (22.6%)	2 (3.2%)
GGT elevation	13 (21.0%)	2 (3.2%)
ALP elevation	10 (16.1%)	–
TBIL elevation	23 (37.1%)	6 (9.7%)
Proteinuria	10 (16.1%)	–

**Abbreviations:** HFS, hand-foot syndrome; Cr, creatinine; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; TBIL, total bilirubin.

**Table 5** Changes in Liver Function at the Beginning and End of Anlotinib Monotherapy

	Before Treatment (n=62)	End of Anlotinib Monotherapy (n=62)	P value
Child-Pugh class (A/B/C)	45/17/0	35/20/7	0.030
ALBI Score	-2.38	-2.16	0.004

Among the Child–Pugh class C patients, three had a Child–Pugh score  $\geq 8$  before medication (Table 5). ALBI scores before anlotinib monotherapy and at the end of treatment/last follow-up were  $-2.38$  and  $-2.16$ , respectively, which was not significantly different ( $P=0.056$ ).

AEs occurred in all 11 patients who changed their treatment regimen to TKIs and PD-1 inhibitors after disease progression, and three patients (27.3%) developed grade  $\geq 3$  AEs.

## Discussion

Anlotinib is a multi-target tyrosine kinase inhibitor with antitumor effects in a variety of solid tumors. Anlotinib has shown good efficacy and tolerability as a first- and second-line treatment of advanced liver cancer, and the incidence of treatment-related AEs appears to be lower for anlotinib than for lenvatinib and regofinib.<sup>16,30,31</sup> In first-line treatment with anlotinib combined with penpulimab in patients with advanced unresectable HCC in China, the ORR was 31.0%, the DCR was 82.8%, and the PFS was 8.8 months,<sup>29</sup> demonstrating efficacy and good safety. The purpose of this study was to investigate the efficacy and safety of anlotinib as a first-line treatment for aHCC in a real-world setting, as well as the efficacy of subsequent treatment after disease progression, to optimize anlotinib-based treatment regimens for aHCC.

Most Phase III clinical studies of TKIs strictly limit the baseline conditions of enrolled patients, such as Child–Pugh class A or Child–Pugh score  $\leq 7$ , platelet count  $\geq 75 \times 10^9$  /L, Hb  $\geq 85$  g/L, bilirubin  $\leq 51.3 \mu\text{mol}$  /L,  $< 50\%$  liver occupation, and without PVT.<sup>13–15,32</sup> However, in the real world, some patients with HCC have PVT, thrombocytopenia, leukopenia, and insufficient functional liver reserve. Effective treatment measures are limited; therefore, TKIs are also being tested in clinical practice in these patients. In this study, the inclusion and exclusion criteria were relatively loose, and the baseline status of the patients was very complicated. Of the patients, 29.0% had tumor occupation  $> 50\%$ , 43.5% had PVT, 29.5% had platelet count  $\leq 75 \times 10^9$  /L, and 13.1% had a decreased white blood cell count; 22.6% of patients had a Child–Pugh score of 8–9; and 50% of patients with platelet count/spleen thickness (PC/SD)  $\leq 1.95$  may have had moderate-to-severe esophageal and gastric varices. The baseline condition of our enrolled patients was relatively poor, and the study results objectively reflect the real-world effects of drug treatment.

Our study found that the mPFS of patients receiving first-line anlotinib monotherapy for aHCC was 7.37 months (95% CI: 5.88–8.86), showing a good therapeutic effect. In the first-line treatment of aHCC, the mTTP of sorafenib was 2.8 months (2.63–3.58) and 5.5 months;<sup>13,14</sup> the mPFS of atezolizumab combined with bevacizumab was 6.8 months,<sup>15</sup> compared with 5.7 months in Chinese patients;<sup>33</sup> lenvatinib's mPFS reached 7.4 months in the REFLECT study<sup>31</sup> and 5.6 months in another study (95% CI 4.3–6.8).<sup>34</sup> Our data suggest that anlotinib is superior to sorafenib for treating aHCC and has comparable mPFS to that previously reported for lenvatinib. Our study found that the CR, ORR, and DCR reached 19.4%, 46.8%, and 87.1%, respectively, in patients with aHCC treated with anlotinib as first-line treatment, which is similar to that reported previously.<sup>28,30</sup> The ORR and DCR for sorafenib were 9.2% and 60.5% and for lenvatinib were 24.1% and 75.5%, respectively.<sup>31</sup> Anlotinib is better than sorafenib as a first-line treatment of patients with aHCC and is not worse than lenvatinib. The reason for the better efficacy found in this study may be that only 12.9% of patients had a dose reduction, and long-term full-dose therapy was very helpful in achieving disease control in these patients.<sup>35</sup> Another reason may be that better management and nursing of patients' hepatitis and cirrhosis allow patients to have sufficient physical condition to receive systemic treatment earlier, which is beneficial for maintaining the Child–Pugh score. Stabilization or reduction of the Child–Pugh score can prolong mPFS, mOS, and post-treatment survival.<sup>36</sup> Third, 51.6% of the patients received local treatment within 1 month of anlotinib treatment. Anlotinib blocks VEGFR at an extremely low half-maximal inhibitory concentration (IC50), which provides efficacy similar to that of

other VEGFR2 inhibitors at low doses.<sup>24,37</sup> Among the factors involved in tumor angiogenesis, VEGFR2 is most closely associated with this process. Anlotinib has wide inhibitory effects and highly inhibits VEGFR2 specifically.<sup>24</sup> Anlotinib can improve tumor immune microenvironment to inhibit tumor growth.<sup>30</sup> This is the basis of Anlotinib's remarkable performance.

AFP is a biomarker for predicting tumor volume reduction in patients with HCC; changes in AFP levels can help clinicians understand the efficacy of treatment,<sup>34,38</sup> with high AFP predictive of poorer OS.<sup>39</sup> We found a median AFP change rate of  $-26.0\%$  ( $-97.0\%$  to  $+135.0\%$ ) after 1 month of anlotinib monotherapy, with AFP levels declining from baseline in  $72.7\%$  of patients. In one study of sorafenib, the AFP decreased from baseline in  $71.0\%$  of patients within 4 weeks of starting treatment;<sup>40</sup> the AFP decreased in  $80.0\%$  ( $12/15$ ) treated with lenvatinib.<sup>41</sup> Therefore, anlotinib monotherapy has a fast response rate, no slower than that of sorafenib and lenvatinib. Therefore, early combination therapy is not recommended. By the time of cutoff, 47 patients ( $75.8\%$ ) were still using anlotinib and 37 patients ( $59.7\%$ ) were still using anlotinib alone. It can be seen that anlotinib monotherapy can control disease well, and the AEs of anlotinib can be tolerated.

The CR was  $21.4\%$ , ORR was  $36.4\%$ , and DCR was  $63.6\%$  in 11 patients who changed the treatment regimen to TKIs combined with PD-1 inhibitors after disease progression. Ak105-203 showed that the ORR and DCR of anlotinib combined with penpulimab as a first-line treatment for patients with aHCC were  $31.0\%$  and  $82.8\%$ , respectively.<sup>29</sup> IMbrave150 showed that the ORR and DCR of atezolizumab combined with bevacizumab as a first-line treatment for patients with aHCC were  $27.3\%$  (95% CI:  $22.5\text{--}32.5$ ) and  $73.6\%$ , respectively.<sup>15</sup> The ORR and DCR of combination therapy in Chinese patients were  $24.6\%$  (95% CI,  $17.5\text{--}32.9\%$ ) and  $70.0\%$  in extended trials.<sup>33</sup> The ORR of lenvatinib combined with CS1003 in patients with unresectable aHCC was  $37.5\%$ <sup>42</sup> and that in combination with pembrolizumab was  $46.0\%$ .<sup>43</sup> These results indicate that changing the treatment regimen to TKIs combined with PD-1 inhibitors can achieve better therapeutic effects after anlotinib monotherapy.

Several studies have examined the safety of anlotinib.<sup>44-46</sup> The common AEs in this study had similar results to those of previous studies on anlotinib, but compared with previous studies, one patient died due to gastrointestinal bleeding in this study. The PC/SD value of 31 cases in the study was  $\leq 1.95$ , and the PC/SD value of this patient was  $1.95$ , which may indicate moderate or severe esophagogastric fundus static varices.<sup>47</sup> Therefore, it cannot be concluded that the bleeding-related death in the patient was completely caused by the side effects of anlotinib; however, it also suggests that we must pay attention to bleeding risk factors in patients when using TKIs. In the IMbrave150 study, the proportion of sorafenib patients, the incidence of grade  $\geq 3$  AEs was  $55.1\%$ , drug withdrawal rate was  $10.3\%$ , dose adjustment or drug interruption was  $60.9\%$ . The incidence of diarrhea was  $49.4\%$  and that of grade  $\geq 3$  was  $5.1\%$ .<sup>33</sup> In the REFLECT study, the incidence of grade  $\geq 3$  AEs was  $75\%$ , drug withdrawal rate was  $9\%$ , and dose reduction rate was  $37\%$  in the lenvatinib group. The incidence of diarrhea was  $39\%$  and that of grade  $\geq 3$  was  $4\%$ .<sup>31</sup> In this study, the incidence of grade  $\geq 3$  AEs was  $38.7\%$  ( $24/62$ ), with 4 patients ( $6.5\%$ ) discontinuing treatment and 8 ( $12.9\%$ ) reducing the dose because of AEs. The incidence of diarrhea during anlotinib treatment was  $33.8\%$ , with no grade  $\geq 3$  diarrhea. The incidence of grade  $\geq 3$  AEs and diarrhea in patients treated with anlotinib is lower than that in patients treated with oral targeted drugs; therefore, patients can take long-term, full doses of anlotinib, which is one reason for the excellent efficacy of anlotinib in patients with advanced HCC.

In conclusion, anlotinib monotherapy has a rapid onset and lasting efficacy, and changing the treatment regimen to TKIs combined with PD-1 inhibitors can also achieve good therapeutic effects after disease progression with anlotinib monotherapy. The treatment of HCC is a long-term process, and the body will face more and larger side effects during the initial combination therapy, which is difficult for patients to tolerate and thus cannot be used for a long time. Moreover, the financial burden on patients is heavy, so we suggest that anlotinib monotherapy should be preferred, and PD-1 inhibitor treatment should be combined after disease progression.

This study has some limitations. First, this was a retrospective study and potential confounding factors could have influenced the results. Second, after progression with anlotinib monotherapy, the sample size of patients treated with TKIs combined with PD-1 blockade therapy was small, and our results require further validation with a larger sample size. Third, most patients were alive at the end of the follow-up, and continued follow-up was required.



## Conclusion

In the real world, anlotinib has shown favorable efficacy and acceptable toxicity as a first-line monotherapy for aHCC. When combined with PD-1 blockade as a second-line treatment, it also exhibits preliminary efficacy and safety. However, more data are required to confirm these observations.

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## Disclosure

The authors declare that they have no competing interests.

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